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10/516,864	03/30/2006	Wen-Luan Wendy Hsiao	32144183.4	8549

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BAKER & MCKENZIE LLP
Pennzoil Place, South Tower
711 Louisiana, Suite 3400
HOUSTON, TX 77002-2716

EXAMINER	
GOLDBERG, JEANINE ANNE	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/516,864	HSIAO ET AL.	
	Examiner	Art Unit	
	Jeanine A. Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/3/04* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed August 6, 2007. Currently, claims 1-29 are pending.

Election/Restrictions

2. Applicant's election with traverse of Group 1, Claims 1-29 directed to gene-encoded beta-catenin in the paper filed August 6, 2007 is acknowledged.

The response asserts that the practice regarding nucleotide sequences permits examination of up to ten sequences as set forth in the 1996 OG notice.

An OG Notice published March 27, 2007 rescinded the 1996 OG Notice that provided for a partial waiver of the requirements for restriction practice by permitting examination of a reasonable number, up to ten, independent and distinct polynucleotide molecules in a single 35 USC 111(a) or 35 USC 371 application. The Notice indicated that the standard of independence and distinctness would be applied to polynucleotide claims filed in an application under 35 USC 111(a). Additionally, the March 27, 2007 OG Notice specifically spoke to the issue of burden of searching more than one independent and distinct invention.

Applicant was provided an opportunity to specifically state on the record that the species were not patentably distinct. "Should applicant traverse on the ground that the inventions or species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions or species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or

admission may be used in a rejection under 35 U.S.C.103(a) of the other invention." Applicants do not appear to have availed them of this opportunity.

The response asserts that election of species practice requires that the examiner must examine all members of the Markush group is the search may be made without serious burden. The response asserts that examination of a gene-encoded beta catenin; a gene-encoded alpha-catenin; and a gene encoded E-cadherin would not place undue burden upon the examiner. This argument has been reviewed but is not considered persuasive because each of these genes encode distinct proteins. Although the applicant asserts that the genes are associated, the genes would require a separate search and examination.

The requirement is still deemed proper and is therefore made FINAL.

Priority

3. This application is a 371 of PCT/US03/20587, filed June 27, 2003 and provisional application 60/392,191, filed June 28, 2002.

Drawings

4. The description of the drawings, page 3 of the specification, does not correspond to the figures. Specifically, in the description, 1a, b, c; 2a, b, c and 3a, b,c, d, e are described. The drawings have 1A, B; 2 A, B, C, D, E; 3 A, B, C, D, E. Therefore, drawings 2d and 2e have not been discussed in the specification and 1C does not appear to exist in the drawings. Appropriate correction is required.

Information Disclosure Statement

5. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Pages 16-17 contains a list of references. Any referecnes appear in the list and not listed on the IDS have not been considered.

Claim Objections

6. Claim 4, 9, 25 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 1 requires beta-catenin and Claim 4 appears to further limit the beta-catenin RNA by changing the gene. This does not further limit the subject matter. Similarly, Claims 9, 14, 19, and 25 are drafted like Claim 4.

7. Claim 1 appears to contain a typographical error. In line 3, the claim recites "serum of plasma". It appears as this should recite "serum or plasma".

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

The claims are broadly drawn to a method for detecting any cancer in any patient by extracting blood serum or plasma and detecting the presence or absence of beta-catenin to determining the presence of cancer based on the detected presence of beta-catenin nucleic acid.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

Adenomas are benign epithelial tumors arising in epithelium of mucosa (stomach, small intestine and bowel), glands (endocrine and exocrine) and ducts. Thus, Adenomas are not cancer.

The art (Wong et al. Clinical Cancer Research, Vol. 10, pages 1613-1617, March 2004) teaches the quantification of plasma b-catenin mRNA in colorectal cancer and adenoma patients. Wong teaches detecting mRNA in plasma in colorectal carcinoma, colorectal adenoma and normal subjects. The results are listed below.

Carcinoma	1480-933100
Adenoma	541-2254
Normal	0-1366

Wong teaches that b-catenin mRNA was detected in the plasma of all 58 colorectal cancer patients; 49 colorectal adenoma patients and 36 or 43 **(84%)** of normal subjects. Thus, the majority of normal patients express b-catenin mRNA in the plasma. Figure 1A illustrates the overlapping ranges of mRNA copies in plasma. Wong states that a more intensive study is necessary to explore whether plasma b-catenin mRNA concentration may be a prognostic factor. Wong further proposes that a large-scale study would be needed to investigate whether plasma b-catenin mRNA might have a role in population screening for colorectal cancer (page 1616, col. 2).

Osman et al (Clin Cancer, Res. Vol. 12, No. 11, pages 3374-3380, June 2006) teaches analysis of biomarkers in the blood for various cancers. Osman teaches testing a hypothesis that blood cell gene expression can differentiate between different cancers as well as between controls. Osman teaches concludes the gene expression patterns found in bladder cancer was distinguishable from other cancers. Thus, Osman teaches an expression pattern for one gene in the blood is not indicative of any cancer.

Fleischhacker et al. (Biocheimica et Biophysica Acta, Vol. 1775, pages 181-232, 2007) provides a review of circulating nucleic acids (CNAs) and ancer. Fleischhacker teaches that contradictory results have been publised between the detection of free-

circulating plams mRNA and clinical data (page 214, col. 2). Fleischhacker teaches the DNA yield from serum is higher than that from plasma (page 219, col. 1).

Guidance in the Specification.

The specification teaches analysis of plasma RNA in carcinoma, adenomas and normal individuals. The results showed that 100% of patients with carcinoma, 11/14 patients with adenoma and 1/10 healthy volunteers carried b-catenin RNA (page 6, lines 19-25). The specification further teaches a quantitative analysis of plasma blood B-catenin RNA. The specification teaches the adenoma b-catenin mRNA was 30 fold higher than in normal individuals.

Carcinoma	6700-44000
Adenoma	690-1800
Normal	0-169

The specification further teaches detection of b-catenin DNA in serum of patients with colorectal adenoma and carcinoma. The specification teaches that serum B-catenin DNA is detectable in all patients with colorectal carcinoma and 9/10 patients with colorectal adenoma, while all 10 healthy individuals were free of serum b-catenin DNA (page 9, lines 12-15).

The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied.

The claims are broadly drawn to **any cancer** however the specification and the art only analyze colorectal cancers. Different cancers have different profiles of expression and copy numbers in the blood plasma or serum. Cancer encompasses colorectal cancer, breast cancer, lung cancer, brain cancer, leukemia, for example. Finding a single transcript in the plasma or the serum does not indicate the patient has any type of cancer. It is unpredictable that the presence of beta-catenin in the blood or plasma is indicate of any cancer. The analysis performed is limited to colorectal cancer. For colorectal cancer, specifically, the art and the specification do not illustrate the presence of beta-catenin is indicative of cancer. The specification describes an individual with beta-catenin detected but was from the normal population. Wong teaches **84% of normal** individuals had beta-catenin detected in the plasma. Moreover, Osman et al teaches analysis of biomarkers in the blood for various cancers. Osman teaches concludes the gene expression patterns found in bladder cancer was distinguishable from other cancers. Thus, Osman teaches an expression pattern for one gene in the blood is not indicative of any cancer. Without further unpredictable and undue experimentation the skilled artisan would be unable to infer from the colorectal analysis performed in the instant specification for the specific beta-catenin nucleic acid any associations with any cancers. Therefore, detecting of any cancer and colorectal cancer in particular would be unpredictable by mere detection of the presence of the beta-catenin nucleic acid in the plasma.

The claims are broadly drawn to **any patient,** as provided in Claim 5, for example. A patient encompasses humans, dogs, and cats among other animals. The instant specification appears to be limited to humans. There is no analysis of expression levels of beta-catenin in dog plasma and any cancer. While the art teaches that dogs suffer from colorectal cancer, there is no indication or expectation that beta-catenin is found in the circulating plasma or serum of dogs. The skilled artisan would be required to determine that the mechanisms of cells in dogs, like human, have circulating DNA and the circulating DNA is expressed in the same proportions as human CANs. Without further experimentation, the skilled artisan would not be able to apply the instant analysis to any patients.

The claims are directed to detecting the presence or absence of beta-catenin nucleic acid. The skilled artisan would be unable to detecting the presence of b-catenin as a positive indicator of cancer because the results illustrate a normal individual with circulating b-catenin. Moreover the art, which appears to be a larger study clearly illustrates that 84% of normal patients were found to have beta-catenin in the plasma. Thus, it would be unpredictable whether any individual with b-catenin in the circulating DNA would determine the presence of the cancer. Since the vast majority of normal individuals in the study of Wong had b-catenin nucleic acid, it is unpredictable how the skilled artisan would distinguish those with cancer from those not having cancer.

Claims 11 and 16 are directed to "beta-catenin associated gene DNA". The response to the restriction requirement asserts that a gene-encoded alpha-catenin; and a gene encoded E-cadherin are associated genes. The instant specification fails to provide any analysis of a gene-encoded alpha-catenin; and a gene encoded E-cadherin and colorectal cancer or any cancer. As noted above, Osman teaches that each gene has different profiles in different cancers and thus would require analysis to confirm the

pattern of the expression. The art similarly fails to provide any analysis. With regard to the quantification claims, there is no analysis of the concentration of the "associated" genes and whether the same ranges are applicable.

Claim 22 is drawn to a quantitative method for detecting beta-catenin based upon ratios. Claim 22 encompasses detecting the absence of carcinoma and adenoma in patients. The claim sets out several values for detecting adenoma , carcinoma or absence of carcinoma/adenoma. The specification and the art teaches a limited number of individuals who had no b-catenin in the plasma. Thus, the normal individuals would have a value of "0". A value of zero in the denominator will not result in a value in any of these ranges, as the value is non-existent. Further, the values provided do not appear to be consistent with the data provided in the art or specification. For example, the median concentration taught in the art for carcinoma patients is 8737. The median value for normal individuals is 291. The ratio would be 8737/291=30. According to the claims, this would be indicative of the presence of adenoma. However, this is carcinoma data.

The concentration taught in the specification for carcinoma patients ranges from 6700-44000 and the range in normal patients is 0-169. The ratio of 6700/169= 39 which is within the range for adenoma. This again provides a results inconsistent with the claims. Therefore, the quantitative ratios provided in the claims to not appear to enable any reliable detection of carcinoma, adenoma or absence of carcinoma/adenoma. The skilled artisan would be unable to use the teachings to accurately determine the status of the patient.

Furthermore, Claim 22 is drawn to serum or plasma levels. Fleischhacker teaches the DNA yield from serum is higher than that from plasma (page 219, col. 1). The instant specification only provides quantitative analysis for plasma. There is not

indication that the serum and plasma levels are in proportion. Therefore, since the art teaches that the serum and plama levels are expected to differ. And there is no teachings how these levels for b-catenin differ, the skilled artisan would be required to perform further experimentation which is unpredictable to determine how the ratios in the different populations range. There is no expectation that the ranges will not be overlapping, as the plama levels are overlapping.

This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the art and the specification do not support the claims. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized difficulties in cancer diagnostics in the serum and plasma. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims1-21 are methods for detecting cancer in a patient by extracting serum or plasma from the patient and detecting beta-catenin. As written the claim is unclear whether the process merely requires detecting beta-catenin in the serum and plasma or whether the claim requires making the association between the presence of the nucleic acid and cancer. The metes and bounds of the claimed invention is unclear. To overcome the instant rejection, the claim could be easily amended to require that "wherein the presence of beta-catenin RNA is indicative of cancer." Similarly, Claims 6, 11, 16 are rejected.

B) Claim 21 is indefinite because colorectal adenoma is not a cancer. Claim 2, 7, 12, or 16 requires that the cancer is colorectal cancer. As noted above, adenomas are benign epithelial tumors arising in epithelium of mucosa (stomach, small intestine and bowel), glands (endocrine and exocrine) and ducts. Thus, Adenomas are not cancer. Thus, the metes and bounds are unclear.

C) Claims 22-25 recites "approximately above" and "approximately 1". The terms are relative terms which renders the claim indefinite. The terms "approximately

above" and "approximately 1" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Conclusion

10. No claims allowable.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

J. Goldberg

Jeanine Goldberg
Primary Examiner
October 5, 2007